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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/843,922	04/30/2001	Masayuki Fukumura	4001-0003CIP	2336

7590 08/10/2005

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 08/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/843,922	FUKUMURA ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/14/05 has been entered.

Claims 1-15 and 19-21 have been cancelled.

Claims 16-18 are presently pending and considered.

Note: Change in Art Unit and SPE

The Examiner has been reassigned to Art Unit 1633. Therefore, future correspondence should reflect such changes. Also, at the end of the Action is the information regarding the SPE of the Art Unit.

Claim Status, Newly-Cancelled Claims

In light of Applicant's cancellation of claims 1-4, 6, 8-11, and 19-21, all rejections and/or objections to such claims are rendered moot, and thus are withdrawn.

Double Patenting, NonStatutory – old rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 16 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of copending Application No. 09/728,207. Although the conflicting claims are not identical, they are not patentably distinct from each other because Claim 16 of the instant application is drawn to any negative strand RNA virus, and Claims 1-3 of copending Application No. 09/728,207 encompass one such virus vector, Sendai virus vectors, comprising deletions of endogenous genes or insertions of exogenous genes. Therefore these claims encompass common subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

In light of Applicant's request (Applicant's response of 5 October 2004, p. 9), this rejection is held in abeyance until such time as otherwise allowable subject matter is established.

Double Patenting, NonStatutory – old rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

In light of Applicant's amendments after final on 4/13/05 the rejection of Claim 16, provisionally rejected under the judicially created doctrine of double patenting over claims 1-3 of copending Application No. 09/720,003, is with drawn.

Double Patenting, NonStatutory – old rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

In light of Applicant's amendments and arguments after final on 4/13/05, the rejections of Claim 16, provisionally rejected under the judicially created doctrine of double patenting over claims 1-6, 8-10, and 14-18 of copending Application No. 09/720,979, is withdrawn.

Double Patenting, NonStatutory – old rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 16 remains provisionally rejected under the judicially created doctrine of double patenting over claim 1 of copending Application No. 10/444,661. This is a provisional double patenting rejection since the conflicting claims have not yet been patented.

In light of Applicant's request (Applicant's response of 5 October 2004, p. 9), this rejection is held in abeyance until such time as otherwise allowable subject matter is established.

Claim Rejections - 35 USC § 112 – written description, readdressed

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

It is noted that the rejection of Claim 16 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, was withdrawn in the Advisory Action of 5/18/05.

Claim Rejections - 35 USC § 112 – enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 16-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a sendai viral vector comprising a heterologous encoding sequence inserted between the R1 and R2 loci, which encodes a protein capable of ~~protecting~~ rodent pyramidal cells of the hippocampus, by direct administration to such cells, ~~from~~ delayed cell death due to short-term ischemic insult, which heterologous encoding sequence encodes FGF-1 or GDNF, does not reasonably provide enablement for any cell type, or any sequence encoding any protein capable of protecting the brain from ischemia. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

It is noted that the Examiner previously indicated, in the advisory action of 5/18/05, that the enablement rejections were overcome, however, further consideration of Applicant's disclosure and the art causes the Examiner to readdress these claims with this rejection.

The Law

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

It is noted that these are factors to be weighed, and not an 8-prong test, and therefore, one factor may override all other factors; or even an outside factor may override all eight factors listed.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its full-claimed scope, and that, therefore, Applicant's claims are not enabled to their full-claimed scope.

The Breadth of the Claims

Applicant's claims encompass sendai viral vectors comprising transgenes for any FGF, NGF, apoptosis inhibitor, heat shock protein, peroxidase, or any neurotrophic factor, which protein is capable of protecting any brain from ischemia.

The breadth of these claims is overly broad, as will be shown below, because Applicant's claimed proteins and genera are not reasonably predicted to protect any brain cells from any animal from ischemia. As such, and as will be shown below, it would undue experimentation for the Artisan to practice the invention within the full scope of invention claimed by Applicant.

The Nature of the Invention

The invention is in the nature of gene therapy to protect any brain cells from any ischemia (cell death). Gene therapy in general is not enabling of new inventions in the field because, for any specific vector and transgene, it is not reasonably predictable, given any particular method of administration, that enough cells will be transformed, and produce enough stable and functional mRNA and protein therefrom, for a long enough period of time to be efficacious.

With regard to gene therapy, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. For example, Deonarain (1998) Expert Opin. Ther. Pat., 8: 53-69, indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequeate levels for a long enough period of time" (p. 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (p. 65, CONCLUSION). Verma (1997) Nature, 389: 239-242, reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (p. 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain

sustained expression ... The use of viruses (viral vectors) is a powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3).

Further, Eck et al. (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, NY., pp. 77-101, states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced, are all important factors for a successful gene therapy (e.g., bridging pp. 81-82). In addition, Gorecki (2001) Expert Opin. Emerging Drugs 6(2): 187-98) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g., ABSTRACT).

Hence, even if a single method of administration is effective with a particular type of transgene and vector, it is not reasonably predictable that another transgene or method of administration would be effective, due to the very nature of gene therapy. Such nature would

lead the Artisan to not to be able to reasonably predict that any particular gene would be produced in enough of the tissue for a long enough period of time to be efficacious.

This is exacerbated by the ischemia. While ischemia may result from temporary occlusion of arteries, as in many rat models, such ischemia usually takes only a week to develop, and given the temporal expression of most gene therapy protocols, such would not also indicate that ischemia due a disease, like Parkinson's disease (Mandel, et al. (2003) CNS Drugs, 17(10): 729-62), would similarly be protected, as the cells in such disease may take decades to die and have complex biochemistries not identical to delayed ischemia due to temporary exclusion of blood supply, and such biochemistries are not even understood at a level that would allow any such prediction (e.g., Mandel, p. 730, paragraph 1). Moreover, due to the complexity of such diseases, the mechanisms of cell death may be so different that rat models like the occlusion of arteries do not accurately reflect the pathology of the diseases, and therefore, such cell death may not be resolved, even if the transgene is expressed long enough. Further, one of Applicant's proteins, GDNF appears to be actually increased in some models of Parkinson's disease (Mandel, p. 739, col. 2, paragraph 3), hence, one of Applicant's example proteins would not necessarily be predicted to prevent Parkinson's, but may cause it.

Further, developing a drug that works in a model does not reasonably correlate to treatment of any animal. Such is because the model may not accurately reflect the biology of the disease in any other animal, and simply because the biochemistry of any animal is particular that animal and not necessarily reflective of all animals. To wit Crystal (1995) Science, 270: 404-410, provides a long list of clinical trials that have yet to yield therapeutic benefits and further states that "humans are not simply large mice." (p. 409). Further underscoring the point that

Crystal made, Gura (1997) Science, 278: 1041-42 states, "the fundamental problem in drug discovery for cancer is that the model systems are not predictive at all." Gura states that they had "basically discovered compounds that were good mouse drugs rather than good human drugs." (p. 1041). Thus, the Artisan could only conclude from any successful results that the method would only work in that particular animal type used, and would not necessarily be efficacious in other animals, such as humans.

Lastly, Applicant's broadly claimed generas, such as, for Example, would not be enabled by a simple demonstration of a single member of the genera. To wit, for example, with fibroblast growth factors, such genera includes over 20 member, which have different splicings within each member, and each splicing has different effects (Nobuyuki, et al. (2004) Trends in Genetics, 20(11): 563-69, pp. 563-64, paragraph bridging). Moreover, any such structural similarity between any two such fibroblast growth factors, may be just that, structural, and the function of such growth factors may differ widely (Id.). Clearly, even though well-established and known, even this genera has such widely-differing effects, that a simple treatment with growth factor does not reflect reasonable predictability with any growth factor.

The State of the Prior Art

The state of the prior art with regard to the paramyxoviridae viruses and the use in transforming neural cells is similarly not enabling of new inventions in the field. While no art of record demonstrates the use of any paramyxoviridae vectors for transforming neural cells, there does exist scant art for the use of sendai viruses in vascular disease and the use of sendai viruses in the form of fusogenic liposomes for the delivery of genes.

Yonemitsu, et al. (2002) Surgery, 131(Supp.1): S261-S268 describes the use of sendai virus vectors in vascular surgery. In Yonemitsu, he echoes some of the concerns addressed in the nature of the invention, above, stating, with regard to previous gene therapy studies, "there are still unsolved issues; the efficacy of these studies largely depends on the gene-transfer efficiency ... The majority of these studies were performed using virus based vectors, and diseased human vasculature possesses several biological barriers to limit gene-transfer efficiency. In fact, gene-transfer efficiencies of adenoviral vectors and recombinant Sendai virus vector were markedly decreased by atherosclerosis or fibromuscular neointima ... the extracellular matrix might thus play a critical role in limiting gene transfer." (p. S262). Essentially, Yonemitsu is recognizing the targeting problem, and that this problem can often be exacerbated when a disease state is present due to histological changes in the tissues. Continuing with his discussion, Yonemitsu further demonstrates that even though VEGF is known to help with angiogenesis, gene therapy to effect the production of VEGF to increase angiogenesis has "many unsolved issues related to the biologica actions of angiogenic growth factors and therapeutic outcome need to be clarified." Again, Yonemitsu recognizes that the use of such vectors is not predictable, even in the face of expressing a protein known to be effective. Yonemitsu concludes by demonstrating some optimism, but a recognition that many problems still need to addressed in order to develop a gene therapy protocol using, *inter alia*, Sendai viral vectors (p. 266). Hence, Yonemitsu, though not even addressing the neural systems of Applicant's invention, evinces many of the same concerns about gene therapy as the nature of the invention. Therefore, the Artisan would not find Yonemitsu enabling of Applicant's invention, drawn to a different tissue and many forms of therapy.

Nakanishi, et al. (1999) Mol. Membr. Biol., 16: 123-27 is similarly not enabling of Applicants invention. Nakanishi provides the use of fusogenic liposomes, the fusion of a sendai virus and a simple liposome to effect gene therapy (p. 123). However, these liposomes are not as fusogenic as ordinary Sendai virus (p. 124). Hence, the Artisan could not reasonably predict from Nakanishi that any Sendai virus would act similarly to the fusogenic liposomes, as far as any targeting were concerned. Moreover, Nakanishi recognizes that the system designed needs further improvements before it will be useful for treating metabolic disorders (p. 126). Hence, even though Nakanishi doesn't even propose applicant's vectors, Nakanishi demonstrates that any Sendai virus vector, even if designed for better vector targeting, is not generally enabled by the state of the art.

The Level of One of Ordinary Skill in the Art at the Time of Invention

The level of one of skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed to its fully-claimed scope without undue experimentation.

The Level of Predictability in the Art

Because the art, as shown above, does not disclose enough information to reasonably predict that any particular genera of protein, within the context of a Sendai vector could protect any brain tissue from any form of ischemia, the Artisan could not predict, in the absence of proof to the contrary, that such applications would be efficacious in any therapeutic application.

Hence, absent a strong showing of guidance and direction and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for its fully claimed scope.

The Direction and Guidance Provided by Applicant

Applicant's disclosure does not provide the information that the Artisan would require to reasonably predict whether any of the protein generas, delivered in a sendai viral vector, through any particular method of administration, would produce an efficacious therapeutic effect, in any particular brain tissue, from any animal, for a long enough period of time to have an efficacious effect.

Applicant's disclosure broadly reviews neurodegenerative diseases and the promise of therapy using various viral vectors (pp. 1-2), including advantages to the use of sendai virus vectors, which are not integrated, therefore not likely to activate cancer genes (but it is also noted that such non-integrated vectors express transgenes only transiently) (p. 2), GDNF and its potential effect on Parkinson's disease (it is noted that such is inconsistent with the finding above that such GDNF is actually increased in certain disease models, and therefore emphasizes the lack of predictability in the field) (p. 2). Further, such evidences the problems with developing a drug within any particular model: if the model is incorrect, then solving the problem in the model does not solve the problem in another animal. Applicant's disclosure also provides a description of the invention, which is to provide Sendai virus vectors for treatment of neural disorders (pp. 2-9), the use of Sendai virus vectors, particularly for delivery to the pyramidal cells of the hippocampus (p. 9), and a broad listing of potential transgenes to deliver via such vectors (p. 10).

However, none of the disclosure allows the artisan to reasonably predict that any particular ischemia can be prevented or treated with any of the transgenes, through delivery of sendai viral vectors by any particular method. Hence, the examples provided by Applicant are required to disclose quite a bit of information, given the breadth of the claims.

The Examples Provided By Applicant

Example 1 demonstrates making Sendai vectors with transgenes. Examples 2-5 demonstrate *in vitro* transformation of cells with Sendai vectors comprising various transgenes, and the subsequent expression of the transgene for up to 10 days. Examples 6-7 demonstrate expression of GFP in mouse and rat brains after stereotactic injection to the pyramidal hippocampus cells of the animals. Example 8 demonstrates similar expression of beta-glucoronidase in deficient mice, with slightly improved behaviors, but such is not predictive of any neuroprotective effect against ischemia. Example 9 demonstrates eating depression in gerbils and rats given similarly administered transgenes of FGF-1,5, and 9, versus a lower level of eat depression in mice given the transgene encoding GFP. Applicant infers that because only hypothalamic nuclei were known at the time to effect such weight control, the cells must necessarily obtain the transgene through diffusion from the pyramidal cells, but such is incorrect: just because it is not known does not mean that pyramidal cells don't effect weight control. Moreover, the GFP itself had an effect. Therefore, it could be the viral vector itself and not just the transgene effecting weight control. Examples 10-11 demonstrate that GDNF and FGF-1 suppress delayed cell death in pyramidal hippocampal cells after such administrations, but does not demonstrate any cell death is prevented, or that any ischemia in any animal can be prevented

with any of the genera embraced by Applicant's claims, given the lack of reasonable predictability in the art, as evidenced above.

Moreover, it is apparent from Applicant's disclosure that Applicant's claims should be limited to pyramidal cells of the hippocampus, as this is Applicant's invention (e.g., EXAMPLE 7), and the fact that only the pyramidal hippocampal cells are shown to be protected in such cases. How such administrations would protect, for example, the substantia nigria, as in Parkinson's disease, given Applicant's disclosure and the Art in general, is beyond the level of reasonable predictability for the Artisan, as reviewed above.

The Quantity of Experimentation Needed to Make and/or Use the Invention

Because of the lack of working examples, insufficient guidance and direction provided by Applicant, the inherent unpredictability of the art, and the nature of the invention, even in the face of an advanced level of skill in the art, one of skill in the art would be required to perform a large amount of experimentation to make use the invention within the full scope as claimed by Applicant. Such experimentation would be required for the Artisan to reasonably predict that any ischemia could be protected, given any particular transgene embraced, in any animal, for any tissue, and any route of administration.

Conclusion

Because of the finding of undue experimentation for the scope of Applicant's claims, Applicant's claims are only enabled for Sendai viral vectors comprising FGF-1 or GDNF transgenes, for direct administration to the pyramidal hippocampal cells, and protection of such cells against delayed cell death due to temporary blood occlusion.

Response to Argument – Enablement

Because the enablement rejection was withdrawn for all aspects except that of treatment of any animal at the Advisory Action of 5/18/05, Applicant's arguments at the after-final response of 4/13/05 are now addressed, to the extent that they remain rejected.

Applicant's response of 4/13/05 has been fully considered but is not found persuasive.

Applicant argues that scaling up is routine in the art, and therefore, given the disclosure of specific *in vitro* and *in vivo* working examples, using models that correlate to mammals other than rodents, Applicant's claims are enabled (Applicant's argument of 4/13/05, p. 19, paragraph 2).

Such is not persuasive. First, scaling up is not referring to larger operations, but to larger animals. Second, it is clear that Applicant's models are not reasonably predicted to correlate, and to make such an assumption in the argument belies the core of the problem: Applicant's treatments are not reasonably predicted to work in other mammals. This is evidenced by the rejections given to date, and re-proffered above with further evidence.

Applicant argues that the Examiner requires a demonstration that such methods would work in humans, and that such is inconsonant with the case law on the subject (Applicant's response of 4/13/05, pp. 19-20, paragraph bridging).

Such is not persuasive. The Examiner has made no such requirement. What is required is for the method to be reasonably predictable. Applicant has not met such requirement.

Applicant argues that the demonstration of *in vivo* and *in vitro* delivery removes all doubt of reasonable correlation to treating neurodegenerative disease such as Parkinson's disease, etc. (Applicant's argument of 4/13/05, paragraph 2).

Such is not persuasive. Simply performing a transformation and expression of gene does not correlate to a treatment. Specifically, the questions remain: does the transgene have a therapeutic effect? For what tissues? Is it expressed for a long enough period of time to effect treatment? Is it reflective of treatment in other animals? These questions, among others, remain unresolved. Therefore simple transformation does not demonstrate efficacious therapy.

Applicant argues that Glorioso, et al. (2003) J. NeuroVirol., 9: 165-72 demonstrates reasonable correlation between animal and human treatment, and even though being post-filing date, demonstrates that the art is reasonably predictable (Applicant's argument of 4/13/05, p. 21, paragraph 1).

Such is not persuasive. Glorioso demonstrates that various particular treatments appear to be likely to treat particular conditions, and that therefore, a number of different viral vectors may be used in appropriate conditions for gene transfer (particular to that treatment) (ABSTRACT). Moreover, Glorioso is far from predicting treatment, as he states "The results of the first human gene therapy trials for neurologic disease, which are just now beginning, will be crucial in defining the next step in the development of this therapy." (ABSTRACT). Also Glorioso states "Although these "proof-of-principle" studies, demonstrate a biological activity of gene transfer, not all of these studies have been correlated with behavioral outcomes that would be required to support the clinical use, and in all these studies the vectors have been injected prior to the ischemic insult, which would severely limit the clinical situations for which such gene transfer would be applicable." (p. 167, col. 1, paragraph 1). Hence, Glorioso is far from stating that such results are reasonably predictive of success, but actually support the Examiner's

contention that such art is not reasonably predictable, and this is even after Applicant's filing date.

Note to Applicant

Applicant may argue that they only wish to obtain viral vectors, and therefore, the claims should be allowed for their full scope. However, Applicant's specification is particularly directed to the use of such vectors in transforming pyramidal cells of the hippocampus (e.g., p. 20, paragraph 2), and therefore, such use must be considered. With regard to the general of such vectors in expressing proteins in any particular cells, Applicant's specification recognizes that such use was already known in the Art, along with the requirements for doing so (e.g., p. 7, paragraph 3). Hence, providing Applicant with patent coverage for such use would be inconsonant with the overall purpose of issuing patents: providing a temporary right of exclusion for the disclosure of a scientific advance. Applicant's scientific advance is the transformation of pyramidal cells with sendai vectors, and not the use of sendai virus as a vector in general, which is already known (above). Therefore, the Examiner does not believe Applicant can obtain coverage for any such proteins encoded by the Sendai virus without a reasonably predictable use for such vectors in transforming pyramidal cells of the hippocampus.

Note: RE Related Art

In order to maintain a clear a record, it is noted that a series of U.S. Patents have issued to Dubensky, Jr., et al., beginning with U.S. Patent No. 5,789,245, which discuss various alphaviruses and layered eukaryotic expression systems. The Dubensky patents, however, while

disclosing the placement of genes, such as FGF (col. 34, paragraph 4), into a Sendai Virus shell (cols. 33-34, paragraph bridging), require that such genes be DNA plasmids and within the context of an alphavirus genome (col. 4, paragraphs 2-3; col. 33, paragraph 5), which does not include the Sendai virus genome. Moreover, Sendai Virus is not disclosed as an alphavirus of the invention, nor is it considered an equivalent (col. 4, paragraphs 2-3). Hence, Dubensky does not teach or suggest placing such transgene into a Sendai viral genome.

Claims Free of the Art

Applicant's claims are free of the art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on (571) 272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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